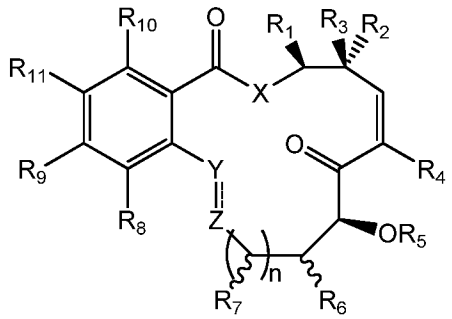
AMENDMENTS TO THE CLAIMS

1. (currently amended) A pharmaceutical composition for systemic administration comprising a pharmaceutically suitable carrier or diluent and a compound having the structure:



or a pharmaceutically acceptable salt or ester thereof; wherein

R_1 is hydrogen, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} heteroalkyl, C_2-C_{20} heteroalkenyl, C_2-C_{20} heteroalkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_3-C_{20} cycloalkynyl, C_3-C_{20} heterocycloalkyl, C_3-C_{20} heterocycloalkenyl, C_3-C_{20} heterocycloalkynyl, C_3-C_{14} aryl or C_3-C_{14} heteroaryl;

R_2 is C_{1-6} alkyl ~~methyl~~;

R_3 is hydrogen, halogen, hydroxyl, protected hydroxyl, or a C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} heteroalkyl, C_2-C_{20} heteroalkenyl, C_2-C_{20} heteroalkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_3-C_{20} cycloalkynyl, C_3-C_{20} heterocycloalkyl, C_3-C_{20} heterocycloalkenyl, C_3-C_{20} heterocycloalkynyl, C_3-C_{14} aryl or C_3-C_{14} heteroaryl moiety; or

R_1 and R_3, when taken together, may form a ~~substituted or unsubstituted,~~ saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

R_4 is hydrogen or halogen;

R_5 is hydrogen or an oxygen protecting group;

R_6 is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R_7, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R_8 is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or a C_1-C_{20} alkyl, C_2-C_{20} alkenyl or C_2-C_{20} alkynyl moiety optionally substituted with hydroxyl, protected hydroxyl, SR_{12}, or $NR_{12}R_{13}$;

R_9 is hydrogen, halogen, hydroxyl, protected hydroxyl, OR_{12}, SR_{12}, $NR_{12}R_{13}$, $-X_1(CH_2)_pX_2$-R_{14}, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or $-X_1(CH_2)_pX_2$-R_{14};

wherein R_{12} and R_{13} are, independently for each occurrence, hydrogen, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} heteroalkyl, C_2-C_{20} heteroalkenyl, C_2-C_{20} heteroalkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_3-C_{20} cycloalkynyl, C_3-C_{20} heterocycloalkyl, C_3-C_{20} heterocycloalkenyl, C_3-C_{20} heterocycloalkynyl, C_3-C_{14} aryl or C_3-C_{14} heteroaryl; or a nitrogen or oxygen protecting group, or R_{12} and R_{13}, taken together may form a saturated or unsaturated cyclic ring of 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R_{12} and R_{13} are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X_1 and X_2 are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X_2-R_{14} together are N_3 or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

R_{14} is hydrogen, or an C_3-C_{14} aryl, C_3-C_{14} heteroaryl, C_1-C_{20}alkyl(C_3-C_{14})aryl, or C_1-C_{20}alkyl(C_3-C_{14})heteroaryl moiety, or is $-(C=O)NHR_{15}$, $-(C=O)OR_{15}$, or $-(C=O)R_{15}$, wherein each occurrence of R_{15} is independently hydrogen, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} heteroalkyl, C_2-C_{20} heteroalkenyl, C_2-C_{20} heteroalkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_3-C_{20} cycloalkynyl, C_3-C_{20} heterocycloalkyl, C_3-C_{20} heterocycloalkenyl, C_3-C_{20} heterocycloalkynyl, C_3-C_{14} aryl or C_3-C_{14} heteroaryl; or R_{14} is $-SO_2(R_{16})$, wherein R_{16} is a C_1-C_{20} alkyl, C_2-C_{20} alkenyl or C_2-C_{20} alkynyl moiety, wherein one or more of R_{14}, R_{15}, or R_{16} are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R_8 and R_9 may, when taken together, form a saturated or unsaturated cyclic ring of 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with

hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

R_{10} is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

R_{11} is hydrogen, hydroxyl or protected hydroxyl;

X is O;

Y is CHR_{17}, C=O, or CR_{17}; and Z is CHR_{18}, C=O, or CR_{18}, wherein each occurrence of R_{17} and R_{18} is independently hydrogen, C_1-C_{20} alkyl, C_2-C_{20} alkenyl or C_2-C_{20} alkynyl wherein Y and Z may be connected by a single or double bond;

wherein oxygen protecting groups are selected from the group consisting of methyl ethers, ~~substituted methyl ethers,~~ methoxymethyl ether, methylthiomethyl ether, benzyloxymethyl ether, p-methoxybenzyloxymethyl ether, ~~substituted~~ ethyl ethers, ~~substituted~~ benzyl ethers, silyl ethers, trimethylsilyl ether, triethylsilylether, triisopropylsilyl ether, t-butyldimethylsilyl ether, tribenzyl silyl ether, t-butyldiphenyl silyl ether, esters, formate, acetate, benzoate, trifluoroacetate, dichloroacetate, carbonates, cyclic acetals and ketals and wherein nitrogen protecting groups are selected from the group consisting of carbamates, Troc, amides, cyclic imides, N-alkyl amines, N-aryl amines, imines, and enamines; and

wherein C_3-C_{14} heteroaryl moieties are selected from cyclic aromatic moieties having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon

~~wherein the compound is present in an amount effective to inhibit production of a pro-inflammatory and/or immunologic cytokine~~.

2. (previously presented) The composition of claim 1, wherein:

R_1 is hydrogen, straight or branched lower alkyl, straight or branched lower heteroalkyl, or C_3-C_{14} aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

R_2 is methyl;

R_3 is hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched lower alkyl, straight or branched lower heteroalkyl, or C_3-C_{14} aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

R_1 and R_3, when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

R_4 is hydrogen or halogen;

R_5 is hydrogen or a protecting group;

R_6 is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R_7, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R_8 is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or lower alkyl optionally substituted with hydroxyl, protected hydroxyl, SR_{12}, or $NR_{12}R_{13}$;

R_9 is hydrogen, halogen, hydroxyl, protected hydroxyl, OR_{12}, SR_{12}, $NR_{12}R_{13}$, $-X_1(CH_2)_pX_2-R_{14}$, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or $-X_1(CH_2)_pX_2-R_{14}$;

wherein R_{12} and R_{13} are, independently for each occurrence, hydrogen, lower alkyl, C_3-C_{14} aryl, C_3-C_{14} heteroaryl, alkyl(C_3-C_{14})aryl, or alkyl(C_3-C_{14})heteroaryl, or a nitrogen or oxygen protecting group, or R_{12} and R_{13}, taken together may form a saturated or unsaturated cyclic ring of 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R_{12} and R_{13} are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X_1 and X_2 are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X_2-R_{14} together are N_3 or are a saturated or unsaturated heterocyclic moiety, p is 2-10, and

R_{14} is hydrogen, or a C_3-C_{14} aryl, C_3-C_{14} heteroaryl, alkyl(C_3-C_{14})aryl, or alkyl(C_3-C_{14})heteroaryl moiety, or is $-(C=O)NHR_{15}$, $-(C=O)OR_{15}$, or $-(C=O)R_{15}$, wherein each occurrence of R_{15} is independently hydrogen, alkyl, heteroalkyl, C_3-C_{14} aryl, C_3-C_{14} heteroaryl, alkyl(C_3-C_{14})aryl, or alkyl(C_3-C_{14})heteroaryl, or R_{14} is $-SO_2(R_{16})$, wherein R_{16} is an alkyl moiety, wherein one or more of R_{14}, R_{15}, or R_{16} are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R_8 and R_9 may, when taken together, form a saturated or unsaturated cyclic ring of 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

R_{10} is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

R_{11} is hydrogen, hydroxyl or protected hydroxyl;

X is O;

Y is CHR_{17}, C=O, or CR_{17}; and Z is CHR_{18}, C=O, or CR_{18}, wherein each occurrence of R_{17} and R_{18} is independently hydrogen or lower alkyl, wherein Y and Z may be connected by a single or double bond.

3. (previously presented) The composition of claim 2, where and n is 1.

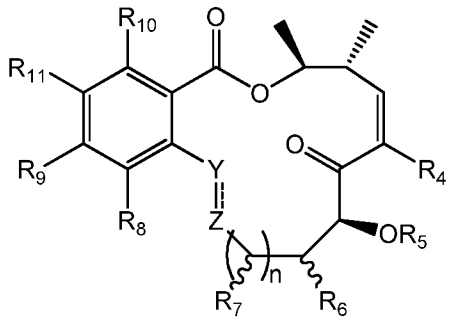
4. (original) The composition of claim 2, where R_4 is halogen.

5. (original) The composition of claim 2, where R_4 is fluorine.

6. (original) The composition of claim 2, where Y and Z together represent -CH=CH-.

7. (original) The composition of claim 2, where Y and Z together represent trans -CH=CH-.

8. (previously presented) The composition of claim 2, wherein R_1 and R_2 are each methyl and R_3 is hydrogen and the compound has the structure:



wherein R_4-R_{11}, n, Y and Z are as defined in claim 2.

9. (previously presented) The composition of claim 8, wherein n is 1.

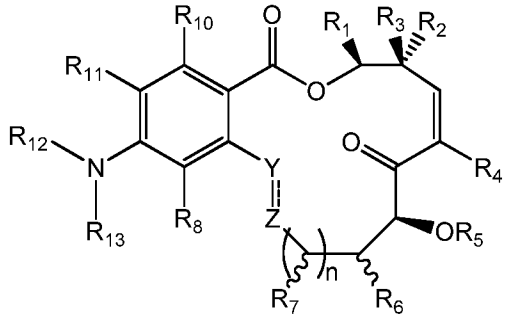
10. (original) The composition of claim 8, wherein R_4 is halogen.

11. (original) The composition of claim 8, wherein Y and Z together represent -CH=CH-.

12. (previously presented) The composition of claim 8, wherein n is 1, R_4 is halogen and Y and Z together represent -CH=CH-.

13. (original) The composition of claim 11 or 12 wherein -CH=CH- is trans.

14. (currently amended) ~~The~~ A pharmaceutical composition ~~of claim 2, wherein R_9 is $NR_{12}R_{13}$~~ for systemic administration comprising a pharmaceutically suitable carrier or diluent and a ~~the~~ compound ~~has~~ having the structure:



or a pharmaceutically acceptable salt or ester thereof; wherein ~~R_1 - R_{13}, n, Y and Z are as defined in claim 2~~

R_1 is hydrogen, straight or branched lower alkyl, straight or branched lower heteroalkyl, or C_3-C_{14} aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

R_2 is C_{1-6} alkyl;

R_3 is hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched lower alkyl, straight or branched lower heteroalkyl, or C_3-C_{14} aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

R_1 and R_3, when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

R_4 is hydrogen or halogen;

R_5 is hydrogen or a protecting group;

R_6 is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R_7, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R_8 is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or lower alkyl optionally substituted with hydroxyl, protected hydroxyl, SR_{12}, or $NR_{12}R_{13}$;

R_{12} and R_{13} are, independently for each occurrence, hydrogen, lower alkyl, C_3-C_{14} aryl, C_3-C_{14} heteroaryl, alkyl(C_3-C_{14})aryl, or alkyl(C_3-C_{14})heteroaryl, or a nitrogen or oxygen protecting group, or R_{12} and R_{13}, taken together may form a saturated or unsaturated cyclic ring of 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R_{12} and R_{13} are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

R_{10} is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

R_{11} is hydrogen, hydroxyl or protected hydroxyl;

X is O;

Y is CHR_{17}, C=O, or CR_{17}; and Z is CHR_{18}, C=O, or CR_{18}, wherein each occurrence of R_{17} and R_{18} is independently hydrogen or lower alkyl, wherein Y and Z may be connected by a single or double bond, or

R_{13} and R_8 may, when taken together, form a cyclic ring of 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydrogen, alkyloxy, amino, alkylamino, aminoalkyl, and halogen;

wherein oxygen protecting groups are selected from the group consisting of methyl ethers, methoxymethyl ether, methylthiomethyl ether, benzyloxymethyl ether, p-methoxybenzyloxymethyl ether, ethyl ethers, benzyl ethers, silyl ethers, trimethylsilyl ether, triethylsilylether, triisopropylsilyl ether, t-butyldimethylsilyl ether, tribenzyl silyl ether, t-butyldiphenyl silyl ether, esters, formate, acetate, benzoate, trifluoroacetate, dichloroacetate, carbonates, cyclic acetals and ketals and wherein nitrogen protecting groups are selected from the group consisting of carbamates, Troc, amides, cyclic imides, N-alkyl amines, N-aryl amines, imines, and enamines; and

wherein C_3-C_{14} heteroaryl moieties are selected from cyclic aromatic moieties having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one

or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon.

15. (previously presented) The composition of claim 14, wherein n is 1.

16. (original) The composition of claim 14, wherein R_4 is halogen.

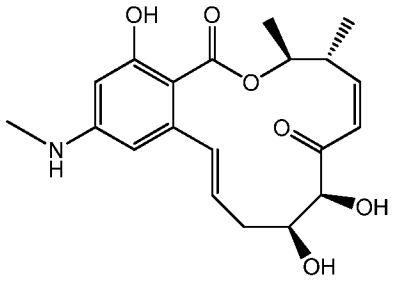
17. (original) The composition of claim 14, wherein Y and Z together represent -CH=CH-.

18. (original) The composition of claim 14, wherein R_1 and R_2 are each methyl and R_3 is hydrogen.

19. (previously presented) The composition of claim 14, wherein n is 1, R_1 and R_2 are each methyl, R_3 is hydrogen, R_4 is halogen, and Y and Z together represent -CH=CH-.

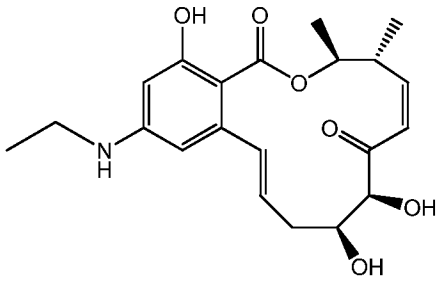
20. (original) The composition of claim 17 or 19, wherein -CH=CH- is trans.

21. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



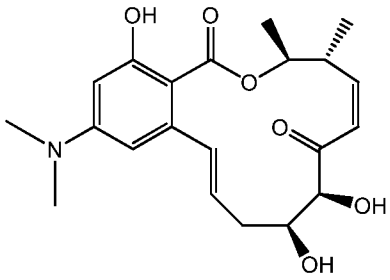
or a pharmaceutically acceptable salt or ester thereof.

22. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



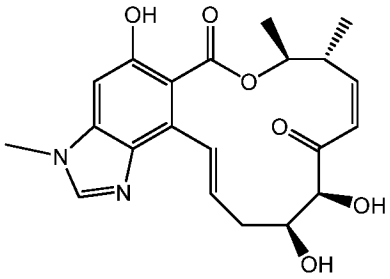
or a pharmaceutically acceptable salt or ester thereof.

23. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

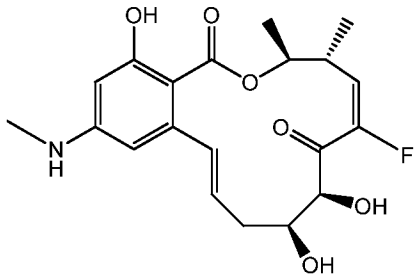
24. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

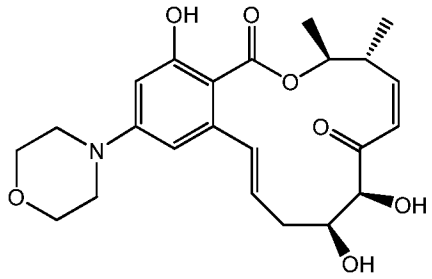
25-26. (canceled)

27. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



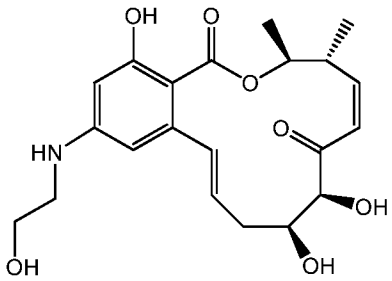
or a pharmaceutically acceptable salt or ester thereof.

28. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



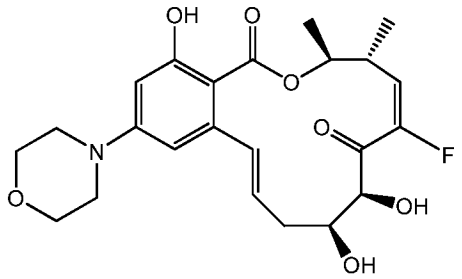
or a pharmaceutically acceptable salt or ester thereof.

29. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



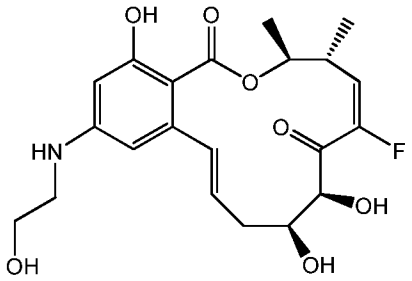
or a pharmaceutically acceptable salt or ester thereof.

30. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

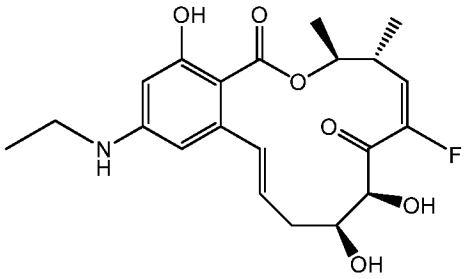
31. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

32. (canceled)

33. (currently amended) The composition of claim [[1]] 14, wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

34-35. (canceled)

36. (withdrawn) The pharmaceutical composition of claim 1, wherein the composition is for oral administration.

37. (canceled)

38. (withdrawn, currently amended) The pharmaceutical composition of claim 1, wherein the compound is present in an amount effective to inhibit production of a ~~the~~ pro-inflammatory and/or immunologic cytokine selected from the group consisting of ~~is~~ TNFα, IL-1, IL-6, IL-8 and ~~or~~ IL-2.

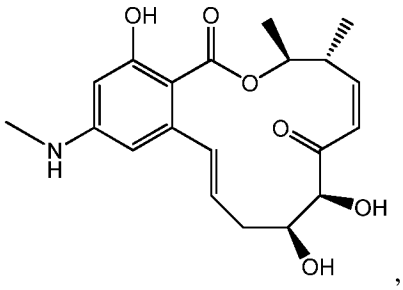
39. (withdrawn) A method for treating rheumatoid arthritis, psoriasis, asthma, sepsis, inflammatory bowel disease, atopic dermatitis or Crohn's disease comprising the step of systemically administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 1.

40. (withdrawn) The method of claim 39, wherein the compound is administered orally.

41. (canceled)

42. (withdrawn) The method of claim 39, wherein the method is for treating psoriasis.

43. (withdrawn) The method of claim 39, wherein the compound has any one of the following structures: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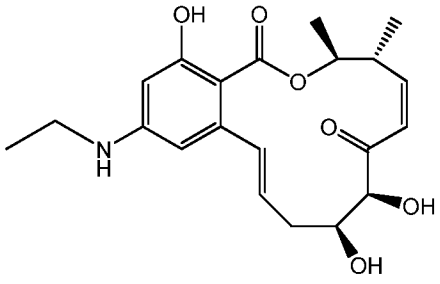
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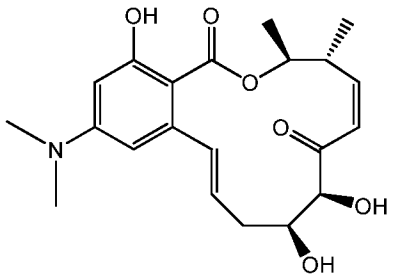
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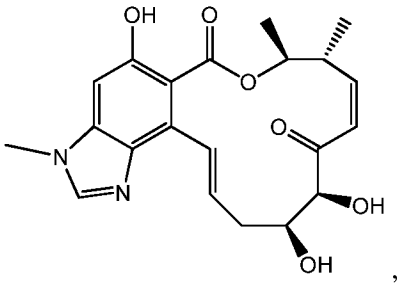
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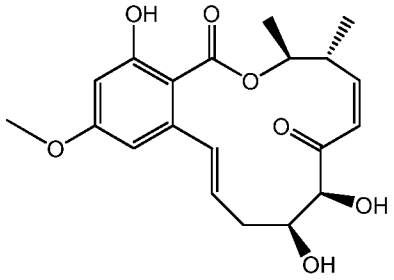
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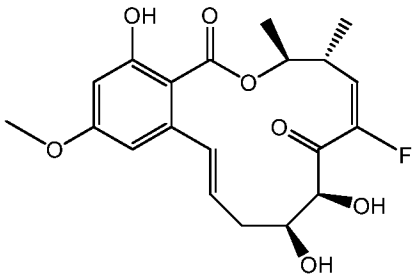
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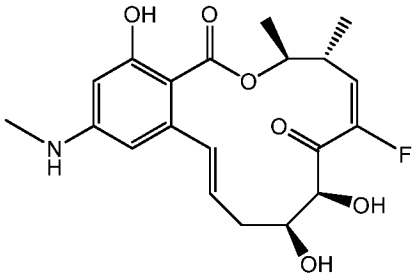
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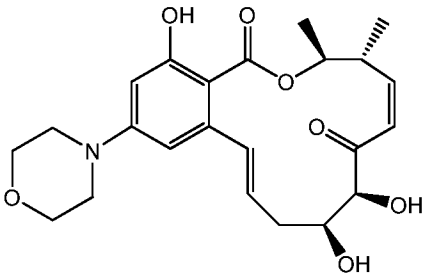
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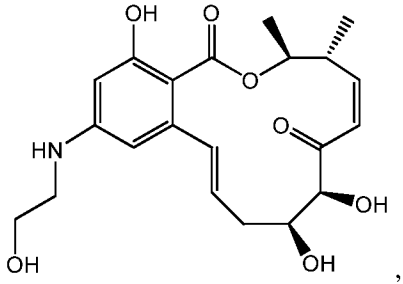
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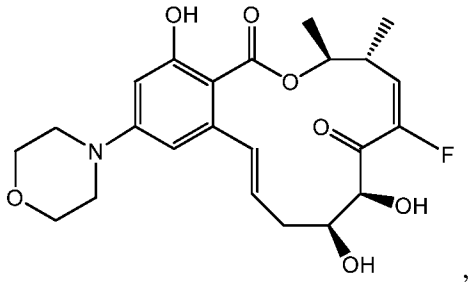
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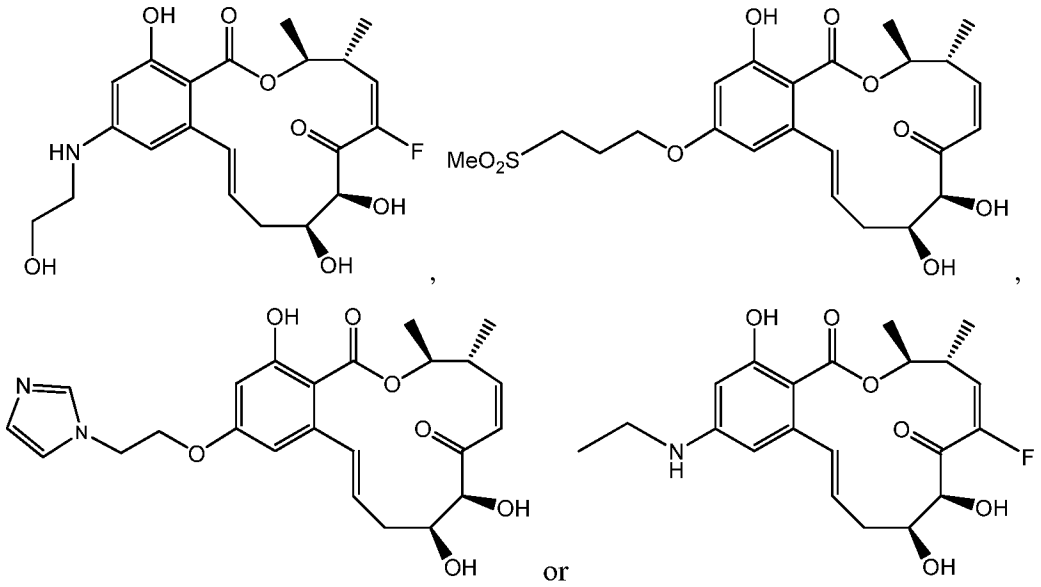


or pharmaceutically acceptable salt or ester thereof.

44-45. (canceled)

46. (withdrawn) The composition of claim 2, where R_1 is hydrogen or methyl.

47. (withdrawn) The composition of claim 2, where R_3 is hydrogen or halogen.

48. (withdrawn) The composition of claim 2, where R_4 is hydrogen.

49. (withdrawn) The composition of claim 2, where R_5 is hydrogen.

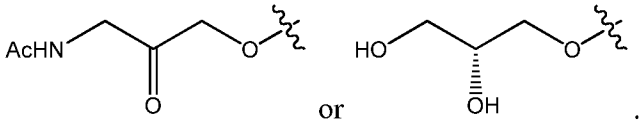
50. (withdrawn) The composition of claim 2, where R_6 is hydroxyl.

51. (withdrawn) The composition of claim 2, where R_7 is hydrogen or hydroxyl.

52. (withdrawn) The composition of claim 2, where R_8 is hydrogen or halogen.

53. (withdrawn) The composition of claim 2, where R_9 is hydroxyl, protected hydroxyl, -OR_{12}, -$NR_{12}R_{13}$, or -$O(CH_2)_pX_2$-R_{14}, wherein R_{12}, R_{13}, R_{14} and X_2 are as defined in claim 2.

54. (withdrawn) The composition of claim 53, where R_9 is $-OR_{12}$, wherein R_{12} is methyl, ethyl, propyl, isopropyl, butyl, $-CH_2COOMe$, Bn, PMB (MPM), 3,4-ClBn, or R_9 is



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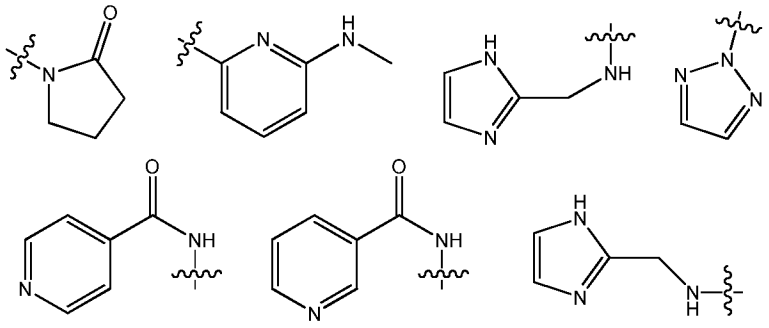
55. (withdrawn) The composition of claim 53, where R_9 is $-NR_{12}R_{13}$, or wherein R_{12} is methyl, ethyl, propyl, isopropyl, or butyl, optionally substituted with one or more occurrences of hydroxyl or protected hydroxyl, and R_{13} is hydrogen or lower alkyl, or $NR_{12}R_{13}$ together represents a 5- or 6- membered heterocyclic moiety.

56. (withdrawn) The composition of claim 53, where R_9 is $-O(CH_2)_pX_2-R_{14}$, wherein X_2-R_{14} together represent N_3, NMe_2, NHAc, $NHSO_2Me$, NHCONHMe, NHCONHPh, morpholine, imidazole, aminopyridine, or any one of:



57. (withdrawn) The composition of claim 2, where R_8 and R_9, taken together, form a saturated or unsaturated cyclic ring of 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen.

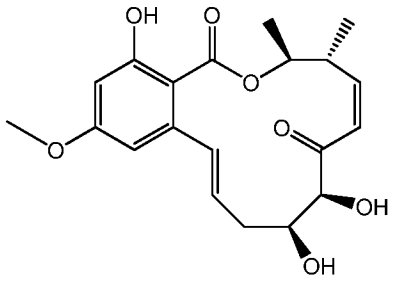
58. (withdrawn) The composition of claim 2, where R_{10} is hydroxyl.

59. (withdrawn) The composition of claim 2, where R_{11} is hydrogen.

60. (withdrawn) The composition of claim 2, where Y and Z together are cyclopropyl.

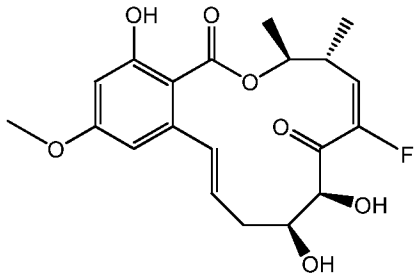
61. (canceled)

62. (currently amended) The composition of claim 1 wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

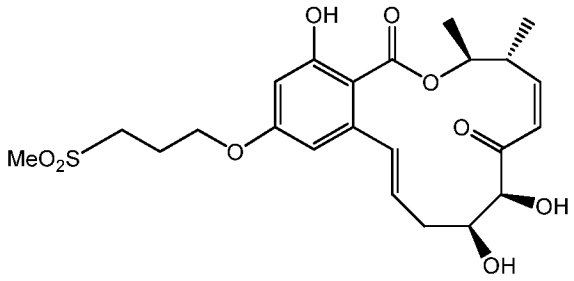
63. (currently amended) The composition of claim 1 wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

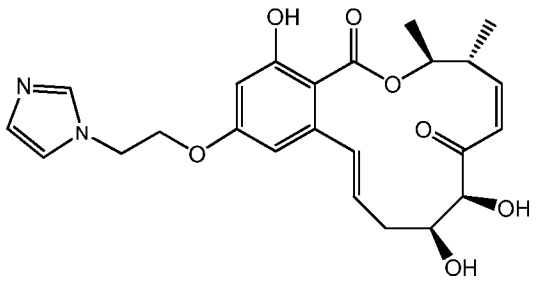
64. (canceled)

65. (currently amended) The composition of claim 1 wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

66. (currently amended) The composition of claim 1 wherein the compound has the structure:



or a pharmaceutically acceptable salt or ester thereof.

67. (new) A pharmaceutical composition for systemic administration comprising a pharmaceutically suitable carrier or diluent and a compound having the structure: